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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/561,108 | 05/11/2006 | Michael D. Burkart | 26774-14255 | 1801 |

758 7590 02/25/2011

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| EXAMINER | |
|---|---|
| KOSSON, ROSANNE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/25/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOC@Fenwick.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/561,108 | BURKART ET AL. | |
| | Examiner | Art Unit | |
| | ROSANNE KOSSON | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-68 and 77-89* is/are pending in the application.

4a) Of the above claim(s) *5,7-12,18-68 and 79-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,13-17,77,78 and 87-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicants' election with traverse of Group 16, claims 1-4, 6, 13, 15-17, 77, 78 and 87-89, as well as claim 14 in part, (drawn to a method of detecting a protein of interest by making a first complex comprising a carrier protein bound to a protein of interest and a second complex comprising a labeled coenzyme, binding the first complex and the second complex, detecting the protein of interest, and contacting the complex of the first and second complexes with coenzyme A or a derivative thereof to form a third complex comprising the carrier protein, the protein of interest, two coenzymes and a label, wherein the carrier protein is non-ribosomal peptide synthase), in the reply filed on January 18, 2011 is acknowledged. Claims 5, 7-12, 18-68 and 79-81, as well as claim 14 in part, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claim 1 has been amended. Claims 69-76 and 82-86 have been canceled. Claims 87-89 have been added. Accordingly, claims 1-4, 6, 13, 15-17, 77, 78 and 87-89, as well as claim 14 in part, are examined on the merits herewith. Claims 16-17 have been rejoined with those of the elected invention, because the prior art discussed below (Mofid et al.), discloses the limitations of these claims and that these steps are involved in labeling the first complex with the second complex.

Regarding claim 14, the claim was restricted and Applicants were required to elect one definite polypeptide (see interview summary of January 28, 2011). Applicants have elected the polypeptide of SEQ ID NO:6 as a polypeptide present in the carrier protein as the elected species for the invention. To the extent that the claim reads on non-elected polypeptides, the claim is withdrawn.

Regarding Applicants' traversal of the restriction requirement, Applicants' arguments are not persuasive. Applicants have amended claim 1 to recite that the carrier protein (or carrier protein domain) is not any protein but may be one of three different proteins. Because these proteins are different proteins, this amendment does not affect the lack of unity of the instant claims. As a result, the restriction requirement is deemed proper and is made final.

***Claim Rejections - 35 USC § 112, first paragraph, Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 13-17, 77, 78 and 87-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a molecule that specifically binds to coenzyme A (such as non-ribosomal peptide synthetase (NRP)), does not reasonably provide enablement for a method of detecting any POI (protein of interest) that binds to any coenzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

First, only one coenzyme is disclosed in the specification, coenzyme A and chemical derivatives thereof (which are labeled versions or versions intended for reacting with a label). Only three proteins that bind to coenzyme A are disclosed in the specification, polyketide synthase, NRP and fatty acid synthase. The specification does not disclose, and the claims do not recite, that the POI specifically binds to the coenzyme A. The claimed method has the additional problem with enablement that the method will detect anything that binds to any

coenzyme (or to coenzyme A), specifically or non-specifically, be it a protein or otherwise. The claimed method will detect far more than the CP/PCP or the molecules that bind to the CP.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue

experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue. The following Wands factors listed above are relevant.

1. Breadth of the claims.

The claims are very broad because they recite a method of detecting any POI by reacting a CP-POI complex with a labeled coenzyme and detecting the label.

3. The state of prior art.

The teachings of Mofid et al. are discussed below. Similar teachings are found in Cane and Walsh and in Du and Shen, ref. nos. 7 and 14 submitted in Applicants' IDS of September 11, 2006. These articles discuss the significance of non-ribosomal peptide synthesis via complexes of modules of C-A-NRP, in which coenzyme A binds to NRP to yield an active holoenzyme.

4. The level of skill in the art.

The level of skill in the art, with respect to the claimed invention, is low, because one skilled in the art would not be able to detect a POI simply by adding a labeled coenzyme to a complex mixture containing a CP-POI complex and anything else, a mixture such as spent culture medium or a cell lysate. He would know how to measure the fluorescence emitted by a sample of the mixture. But, he would know that that sample measurement indicates nothing in

particular.

6 - 7. The amount of guidance present and working examples.

Applicants have provided guidance for one structure and methods of using it, a structure in which coenzyme A is bound to the PCP moiety. The coenzyme A has a linker attached to the terminus distal from the PCP (the thiol group), with a fluorescent label bound to the linker (see Figs. 1-10). Examples 3 and 5 on pp. 20-24 disclose that a CP-POI complex can be detected by detecting the label only after several additional separation and purification steps not recited in the claims. A cell lysate comprising the recombinantly made CP VibB was labeled with labeled coenzyme A. The labeled mixture was dialyzed to remove the smaller molecules. Samples of the remainder were run on an SDS-PAGE gel. Fluorescent bands were cut out and analyzed.

5 and 8. Predictability and the amount of additional experimentation required.

The specification discloses that a CP linked to fluorescently labeled coenzyme A, after purification of the CP from a mixture of other molecules, can be detected by detecting the fluorescence of the labeled construct. It is not clear what part of VibB is the POI. But, the specification does not disclose that any POI may be detected by contacting a composition comprising the POI, even as a CP-POI complex, with any labeled coenzyme.

Consequently, the teachings in the specification and the prior art do not allow one skilled in the art to predict that Applicants' method can be carried out as claimed. Because the claimed method is not predictable, i.e., because one skilled in the art cannot predict that the method as claimed can be accomplished, undue experimentation is required to determine whether or not Applicant's method can be practiced as claimed.

Without sufficient guidance, which has not been provided, practicing the claimed method is unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and

improperly, extensive and undue. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 13-17, 77, 78 and 87-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and some of its dependent claims, e.g., claims 3 and 13, recite the limitations of any POI and any coenzyme. The claims are indefinite, because not all proteins (a POI can be any protein) and coenzymes will work in the claimed method, and it cannot be determined from the claims which ones are meant. Clarification and appropriate correction are required.

Claim 13 is confusing, because it cannot be determined how contacting two proteins (the CP and the POI) forms a fusion protein from them. It cannot be determined how contacting two proteins "further comprises synthesizing" a fusion protein. A fusion protein is made at the DNA level, i.e., two genes are joined together in the same construct. Clarification and appropriate correction are required.

In claim 14, the limitation "consensus sequence" is confusing, because the claim recites no consensus sequence. The sequence listing makes it clear that each pair of brackets, separated by a dash, represents a variable and contains a set of amino acids that may be used as that variable. No amino acid position is represented by a constant amino acid. The claim

recites an enormous number of polypeptides, but these polypeptides have no structure common to all of them. Clarification and appropriate correction are required.

Cls. 13-16, 87 and 88 are confusing, because they recite the terms "further comprising" or "further comprises." Applicants appear to mean simply "comprising" or "comprises," as these claims specify portions of the claims that they depend from. For example, claim 15 specifies that the coenzyme is coenzyme A or a derivative thereof. Claim 88 specifies that a coenzyme A derivative, not any coenzyme, is reacted with the CP-POI complex. It is unclear if such is the intended meaning or if Applicants mean, e.g., in claims 15, 87 and 88, that the labeled coenzyme-CP-POI complex contains two coenzymes, any coenzyme and a coenzyme A derivative. Nevertheless, an interpretation is required to proceed with prosecution. The claims have been interpreted to mean the former, because the CP (NRP) does not have two or multiple binding sites for coenzyme A. Clarification and appropriate correction are required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 13, 15-17, 77, 78 and 87-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mofid et al. ("Recognition of hybrid peptidyl carrier proteins/acyl carrier proteins in nonribosomal peptide synthetase modules by the 4'-phosphopantetheinyl transferases AcpS and Sfp," J Biol Chem 277(19):17023-17031, 2002), in view of Belshaw et al. ("Aminoacyl-coAs as probes of condensation domain selectivity in nonribosomal peptide synthesis, Science 284:486-489, 1999); and Fuma et al. (GenBank record no. BAA02522, surfactin synthetase, *Bacillus subtilis*, January 2003). Mofid et al. and Belshaw et al. were filed in Applicants' IDS of September 11, 2006.

Mofid et al. disclose the mechanism present in bacteria and fungi for synthesizing polypeptides independently of protein translation. These polypeptides represent a large number of anti-microbial agents. In this mechanism, a carrier protein domain (a CP), having peptidyl carrier protein activity (PCP activity), the protein non-ribosomal peptide synthetase (NRP), is contacted with (and binds to) a protein of interest (a POI), the protein called the adenylation domain or A, forming a CP-POI complex. A 4'-phosphopantetheinyl transferase (PPTase) converts the apo-PCP to the holo-PCP form by binding a coenzyme (coenzyme A) to the PCP, forming a phosphoester of the coA (coenzyme A) linked to the PCP. The PCP and the POI are biosynthetic enzymes, as their role is to make polypeptides (see pp. 17023-17025). See claims 1-4, 6, 15, 77 and 78. Because the PCP and POI bind when they are contacted, they fuse, as part of forming a module, forming a fusion protein (see p. 17024, left col.) (see claim 13).

Regarding claim 14, Fuma et al. disclose that Applicants' SEQ ID NO:6 corresponds to amino acids 1001-1016 in their polypeptide, a surfactin synthetase, which comprises CP/NRP

domains and coenzyme A/phosphopantetheine attachment domains. The region of amino acids 1001-1016 is in a coenzyme A binding site (see pp. 2 and 3).

Regarding claims 15 and 87-89, Mofid et al. do not disclose that the coA is a coA derivative, i.e., a derivatized form comprising a label, in particular a fluorescent label, and a linker.

Belshaw et al. disclose that coA may be exposed to derivatizing agents so as to form fluorescent derivatives, via a reaction at the thiol end. The reaction of coA with an amino acid linked to an Nvoc (6-nitroveratryloxycarbonyl) group yields a coA derivative comprising a linker (the amino acid) and a fluorescent label (Nvoc; nitro groups and phenyl groups are fluorescent). These labeled coA derivatives bind to PCP's (see p. 486 and p. 487, left col.) (claims 15 and 87-89).

It would have been obvious to the artisan of ordinary skill at the time of the invention to make the CP/NRP and A/POI proteins of Mofid et al. recombinantly, either separately or as a fusion protein, to make a CP-POI complex, because the artisan of ordinary skill would have known that this complex could have been used to synthesize a variety of anti-microbial agents in vitro. Mofid et al. disclose that the genes and protein sequences for these C, A and PCP complexes were known at the time of the invention (see p. 17024, right col.; and p. 17026). Additionally, it would have been obvious to the artisan of ordinary at the time of the invention to make a CP that comprises Applicants' SEQ ID NO:6, because Fuma et al. disclose that this polypeptide is part of a coenzyme A binding site. Mofid et al. disclose that a coA binding site is needed for the CP to work, i.e., for it to become an active holoenzyme.

The claimed method is obvious, because it would have been obvious to the artisan of ordinary skill at the time of the invention to label the CP-POI complex, in order to detect the CP-POI complex once it was made, in order to detect its presence, qualitatively and quantitatively,

and to purify it from a host cell culture medium (or fermentation broth) or from a culture of the host cells that made the proteins. Mofid et al. disclose that coA is a ligand for the CP/PCP. Thus, it would have been obvious to the artisan of ordinary skill to add an easily detectable label, such as a fluorescent label, to this ligand (claims 1, 16 and 17).

Regarding claims 15, 16, 87 and 88, which recite "further comprising" or "further comprises" (as discussed above, these terms are considered to mean comprising or comprises), even if taken to mean do it a second time, it would have been obvious to the artisan of ordinary skill at the time of the invention to run the PPTase-catalyzed binding reaction between the CP-POI complex and the fluorescently labeled coA multiple times with additional labeled coA, or to run the reaction until it was complete, allowing the molecules to react multiple times. The term "further comprising" in these claims encompasses repeating the binding reaction. This limitation is an obvious one, because the artisan of ordinary skill would have known that it would have been desirable to have CP-POI complexes that are as highly labeled as possible for maximal detection.

In view of the foregoing, a holding of obviousness is required. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROSANNE KOSSON whose telephone number is (571)272-2923. The examiner can normally be reached on Mon., Tues., Fri., 8:30-6:00, Thurs., 8:30-2:00, Wed. off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rosanne Kosson/
Examiner, Art Unit 1652
2011-02-15